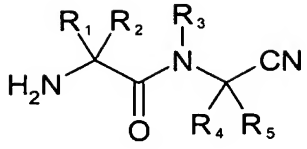
Claims

1. A compound of formula (I)



(I)

or a pharmaceutically acceptable salt or prodrug thereof, wherein

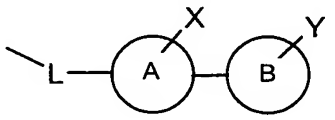
R_1 is hydrogen, C_{1-6}alkyl optionally substituted with a substituent selected from the group consisting of halogen, amino, hydroxy, cyano and C_{1-3}alkoxy; or C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}alkoxy, C_{1-6}alkylthio, C_{1-6}alkylcarbonyl, an unsubstituted or substituted C_{3-10}cycloalkyl group, an unsubstituted or substituted C_{3-10}cycloalkylcarbonyl group, an unsubstituted or substituted C_{5-10}cycloalkenyl group, an unsubstituted or substituted C_{3-7}heterocycloalkyl group, an unsubstituted or substituted C_{1-6}alkylaryl group, an unsubstituted or substituted C_{2-6}alkenylaryl group, an unsubstituted or substituted C_{1-6}alkylheteroaryl group, an unsubstituted or substituted aryl group, an unsubstituted or substituted heteroaryl group, an unsubstituted or substituted aroyl group, an unsubstituted or substituted arylthio group, an unsubstituted or substituted aryloxy group, an unsubstituted or substituted arylsulfonyl group, an unsubstituted or substituted arylamino group, an unsubstituted or substituted heteroaroyl group, an unsubstituted or substituted heteroaryloxy group, an unsubstituted or substituted heteroarylsulfonyl group, an unsubstituted or substituted heteroarylamino group, an unsubstituted or substituted C_{1-5}alkylC_{3-7}cycloalkyl group or an unsubstituted or substituted C_{1-5}alkylC_{3-7}heterocycloalkyl group;

R_2 is hydrogen or C_{1-6}alkyl; or R_1 and R_2 together form an unsubstituted or substituted C_{3-10}cycloalkyl group or an unsubstituted or substituted C_{3-7}heterocycloalkyl group;

R_3 is hydrogen or C_{1-6}alkyl; or R_1 and R_3 together form an unsubstituted or substituted C_{3-7}heterocycloalkyl group;

R_4 is hydrogen, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}alkoxy, C_{1-6}alkylthio, C_{1-6}alkylcarbonyl, C_{1-6}alkylsulfonyl, an unsubstituted or substituted C_{3-10}cycloalkyl group,

an unsubstituted or substituted C_{3-10}cycloalkylcarbonyl group, an unsubstituted or substituted C_{5-10}cycloalkenyl group, an unsubstituted or substituted C_{3-7}heterocycloalkyl group, an unsubstituted or substituted C_{1-6}alkylaryl group, an unsubstituted or substituted C_{2-6}alkenylaryl group, an unsubstituted or substituted C_{1-6}alkylheteroaryl group, an unsubstituted or substituted aryl group, an unsubstituted or substituted heteroaryl group, an unsubstituted or substituted aroyl group, an unsubstituted or substituted arylthio group, an unsubstituted or substituted aryloxy group, an unsubstituted or substituted arylsulfonyl group, an unsubstituted or substituted arylamino group, an unsubstituted or substituted heteroaroyl group, an unsubstituted or substituted heteroaryloxy group, an unsubstituted or substituted heteroarylsulfonyl group, an unsubstituted or substituted heteroarylamino group, an unsubstituted or substituted C_{1-5}alkylC_{3-7}cycloalkyl group or an unsubstituted, substituted C_{1-5}alkylC_{3-7}heterocycloalkyl group or a group of the formula :



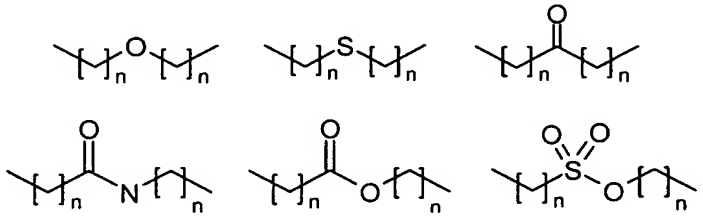
wherein A is a ring system with one ore more substituents X, and A is selected from C_{5-7}cycloalkyl, C_{5-7}heterocycloalkyl, aryl and heteroaryl;

X being the same or different selected from hydrogen, Cl, Br, F, I, hydroxy, amino, cyano, trifluoromethyl, C_{1-6}alkyl, C_{1-6}alkylthio or C_{1-6}alkoxy;

B is a ring system with one ore more substituents Y, and B is selected from C_{5-7}cycloalkyl, C_{5-7}heterocycloalkyl, aryl and heteroaryl;

Y being the same or different selected from hydrogen, Cl, Br, F, I, hydroxy, amino, cyano, trifluoromethyl, C_{1-6}alkyl, C_{1-6}alkylthio or C_{1-6}alkoxy;

-L- is a linker, which is C_{1-6}alkyl or C_{2-6}alkenyl, or a moiety selected from the group consisting of



and, wherein the linker -L- may be attached *via* either of the two free bonds to the ring A;

n is the same or different integer selected from 0, 1, 2 and 3;

R_5 is hydrogen or C_{1-6}alkyl; or R_4 and R_5 together form an unsubstituted or substituted C_{3-10}cycloalkyl group or an unsubstituted or substituted C_{3-7}heterocycloalkyl group;

wherein a substituted group is substituted with one, two or three substituents independently selected from the group consisting of C_{1-6}alkyl, C_{1-6}alkoxy, C_{1-6}alkylthio, C_{1-6}alkylcarbonyl, C_{1-6}-N-alkylamide, dialkylamino-C_{1-6}alkyl, amide, hydroxy, carboxy, amino, nitro, halogen, trifluoromethyl, trifluoromethoxy, trifluoromethylthio and cyano.

2. A compound according to claim 1, wherein R_1 is selected from the group consisting of hydrogen, C_{1-6}alkyl, an unsubstituted or substituted aryl, an unsubstituted or substituted C_{1-6}alkylaryl group, an unsubstituted or substituted C_{1-6}alkylheteroaryl group, or an unsubstituted or substituted C_{3-10}-cycloalkyl group.

3. A compound according to claim 1 or 2, wherein R_1 is hydrogen, methyl, ethyl, *n*-propyl, isopropyl, n-butyl, isobutyl, *sec*-butyl, *tert*-butyl, phenyl, benzyl or cyclohexyl.

4. A compound according to any of claims 1-3, wherein R_1 is hydrogen, methyl or ethyl.

5. A compound according to claim 1, wherein R_1 and R_2 together form an unsubstituted or substituted C_{3-10}cycloalkyl group or an unsubstituted or substituted C_{3-7}heterocycloalkyl group.

6. A compound according to claim 1 or 5, wherein R_1 and R_2 together form an unsubstituted or substituted cyclohexyl group.

7. A compound according to claim 1, wherein R_1 and R_3 together form an unsubstituted or substituted C_{3-7}heterocycloalkyl group.

8. A compound according to claim 1 or 7, wherein R_1 and R_3 together form a pyrrolidonyl or piperidonyl.

9. A compound according to any of claims 1-4, 7-8, wherein R_2 is hydrogen.

10. A compound according to claim 1, wherein R_3 is hydrogen or methyl.

11. A compound according to any of the preceding claims, wherein R_4 is selected from the group consisting of hydrogen, C_{1-6}alkyl, an unsubstituted or substituted C_{1-6}alkylaryl group, an unsubstituted or substituted C_{1-6}alkenylaryl group and an unsubstituted or substituted C_{1-6}alkylheteroaryl group.

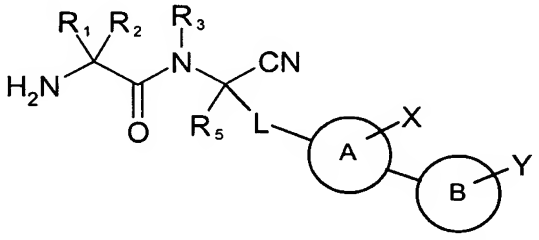
12. A compound according to any of the preceding claims, wherein R_4 is hydrogen, unsubstituted or substituted benzyl, 2-phenylethyl, 3-phenylprop-2-ene, [1,1'-biphenyl-4-yl]methyl or [1,1'-biphenyl-2-yl]methyl.

13. A compound according to any of the preceding claims, wherein R_5 is hydrogen.

14. A compound according any of claims 1-10, wherein R_4 and R_5 together form an unsubstituted or substituted C_{3-10}cycloalkyl group or an unsubstituted or substituted C_{3-7}heterocycloalkyl group.

15. A compound according to any of claims 1-13, wherein at least one of R_4 and R_5 is hydrogen.

16. A compound according to any of claims 1-10, 13, 15 with the following structure



wherein R1, R2, R3, R5, A, B, X, Y and L are defined in claim 1.

17. A compound according to any of claims 1-10, 13, 15, 16, wherein R_4 is [1,1'-biphenyl-4-yl]methyl, [1,1', 2-methylbiphenyl-4-yl]methyl, [1,1', 3-methylbiphenyl-4-yl]methyl, [1,1', 2-hydroxybiphenyl-4-yl]methyl, [1,1', 3-hydroxybiphenyl-4-yl]methyl, [1,1', 2-methoxybiphenyl-4-yl]methyl, [1,1', 3-methoxybiphenyl-4-yl]methyl, [1,1', 2-methylthiobiphenyl-4-yl]methyl, [1,1', 3-methylthiobiphenyl-4-yl]methyl, [1,1', 2-cyanobiphenyl-4-yl]methyl, [1,1', 3-cyanobiphenyl-4-yl]methyl, [1,1', 2-aminobiphenyl-4-yl]methyl, [1,1', 3-aminobiphenyl-4-yl]methyl, [1,1', 2-fluorobiphenyl-4-yl]methyl, [1,1', 3-fluorobiphenyl-4-yl]methyl, [1,1', 2-chlorobiphenyl-4-yl]methyl, [1,1', 3-chlorobiphenyl-4-yl]methyl, [1,1', 2-bromobiphenyl-4-yl]methyl, [1,1', 3-bromobiphenyl-4-yl]methyl, [1,1',

2'-fluorobiphenyl-4-yl]methyl, [1,1', 3'-fluorobiphenyl-4-yl]methyl, [1,1', 4'-fluorobiphenyl-4-yl]methyl, [1,1', 2'-chlorobiphenyl-4-yl]methyl, [1,1', 3'-chlorobiphenyl-4-yl]methyl, [1,1', 4'-chlorobiphenyl-4-yl]methyl, [1,1', 2'-bromobiphenyl-4-yl]methyl, [1,1', 3'-bromobiphenyl-4-yl]methyl, [1,1', 4'-bromobiphenyl-4-yl]methyl, [1,1', 2'-cyanobiphenyl-4-yl]methyl, [1,1', 3'-cyanobiphenyl-4-yl]methyl, [1,1', 4'-cyanobiphenyl-4-yl]methyl, [1,1', 4'-hydroxybiphenyl-4-yl]methyl, [1,1', 4'-aminobiphenyl-4-yl]methyl, [1,1', 4'-methoxybiphenyl-4-yl]methyl, [1,1', 4'-methylthiobiphenyl-4-yl]methyl, [1,1', 4'-trifluoromethylbiphenyl-4-yl]methyl, [1,1', 2-methyl-4'-fluorobiphenyl-4-yl]methyl, [1,1', 2-chloro-4'-cyanobiphenyl-4-yl]methyl, [1,1', 2-methoxy-3'-fluorobiphenyl-4-yl]methyl, [1,1', 2-hydroxy-2'-fluorobiphenyl-4-yl]methyl, [1,1', 3-amino-3'-methoxybiphenyl-4-yl]methyl, [1,1', 2-fluoro-4'-fluorobiphenyl-4-yl]methyl [2-phenyl-1,3-thiazol-4-yl]methyl, [5-phenylpyridin-3-yl]methyl, [3-pyrimidin-5-ylphenyl]methyl, [3-pyridin-2-ylphenyl]methyl, [3-pyridin-4-ylphenyl]methyl, [3-(1H-indol-6-yl)phenyl]methyl, [1-(2-fluorophenyl)piperidin-4-yl]methyl, [3-fluoro-4-(1-piperidinyl)phenyl]methyl, [1,1'-biphenyl-4-yl]ethyl, [1,1', 2-methylbiphenyl-4-yl]ethyl, [1,1', 3-methylbiphenyl-4-yl]ethyl, [1,1', 2-hydroxybiphenyl-4-yl]ethyl, [1,1', 3-hydroxybiphenyl-4-yl]ethyl, [1,1', 2-methoxybiphenyl-4-yl]ethyl, [1,1', 3-methoxybiphenyl-4-yl]ethyl, [1,1', 2-methylthiobiphenyl-4-yl]ethyl, [1,1', 3-methylthiobiphenyl-4-yl]ethyl, [1,1', 2-cyanobiphenyl-4-yl]ethyl, [1,1', 3-cyanobiphenyl-4-yl]ethyl, [1,1', 2-aminobiphenyl-4-yl]ethyl, [1,1', 3-aminobiphenyl-4-yl]ethyl, [1,1', 2-fluorobiphenyl-4-yl]ethyl, [1,1', 3-fluorobiphenyl-4-yl]ethyl, [1,1', 2-chlorobiphenyl-4-yl]ethyl, [1,1', 3-chlorobiphenyl-4-yl]ethyl, [1,1', 2-bromobiphenyl-4-yl]ethyl, [1,1', 3-bromobiphenyl-4-yl]ethyl, [1,1', 2'-fluorobiphenyl-4-yl]ethyl, [1,1', 3'-fluorobiphenyl-4-yl]ethyl, [1,1', 4'-fluorobiphenyl-4-yl]ethyl, [1,1', 2'-chlorobiphenyl-4-yl]ethyl, [1,1', 3'-chlorobiphenyl-4-yl]ethyl, [1,1', 4'-chlorobiphenyl-4-yl]ethyl, [1,1', 2'-bromobiphenyl-4-yl]ethyl, [1,1', 3'-bromobiphenyl-4-yl]ethyl, [1,1', 4'-bromobiphenyl-4-yl]ethyl, [1,1', 2'-cyanobiphenyl-4-yl]ethyl, [1,1', 3'-cyanobiphenyl-4-yl]ethyl, [1,1', 4'-cyanobiphenyl-4-yl]ethyl, [1,1', 4'-trifluoromethylbiphenyl-4-yl]ethyl, [1,1', 2-methyl-4'-fluorobiphenyl-4-yl]ethyl, [1,1', 2-chloro-4'-cyanobiphenyl-4-yl]ethyl, [1,1', 2-methoxy-3'-fluorobiphenyl-4-yl]ethyl, [1,1', 2-hydroxy-2'-fluorobiphenyl-4-yl]ethyl, [1,1', 3-amino-3'-methoxybiphenyl-4-yl]ethyl, [2-phenyl-1,3-thiazol-4-yl]ethyl, [5-phenylpyridin-3-yl]ethyl, [3-pyrimidin-5-ylphenyl]ethyl, [3-pyridin-2-ylphenyl]ethyl, [3-pyridin-4-ylphenyl]ethyl, [3-(1H-indol-6-yl)phenyl]ethyl, [1-(2-fluorophenyl)piperidin-4-yl]ethyl, [3-fluoro-4-(1-piperidinyl)phenyl]ethyl, [1,1'-biphenyl-4-yl]methyloxymethyl, [1,1',4'-fluorobiphenyl-4-yl]methyloxymethyl, [1,1'-biphenyl-4-yl]methylthiomethyl, [1,1',4'-fluorobiphenyl-4-yl]methylthiomethyl, [1,1'-biphenyl-4-yl]ethylenyl or [1,1',4'-fluorobiphenyl-4-yl]ethylenyl.

18. A compound according to claim 1, selected from the group consisting of
N-(2*S*-2-amino-3-phenylpropionyl)-aminoacetonitrile;
(2*S*)-*N*-[(2*S*)-2-aminobutanoyl]-2-amino-3-phenylpropionitrile;
(2S)-N-Methyl-N-[(2S)-2-aminobutanoyl]-2-amino-3-phenylpropionitrile;
(2S)-N-[(2S)-2-aminobutanoyl]-2-amino-3-(p-chlorophenyl)propionitrile;
(2S)-N-[(2S)-2-aminobutanoyl]-2-amino-3-(1,1'-biphenyl-4-yl)propionitrile;
(2S)-(4Z)-N-[(2S)-2-aminobutanoyl]-2-amino-5-phenyl-pent-4-ene-nitrile;
(2S)-N-[(2S)-2-aminobutanoyl]-2-amino-4-phenylbutyronitrile and
(2S)-N-[(2S)-3-phenylaminopropanoyl]-2-amino-3-phenylpropionitrile.

19. The compound according to claim 1, which exhibits an IC_{50} value of 500 μM or less such as, e.g., 100 μM or less, 50 μM or less, 1 μM or less, 500 nM or less, 100 nM or less, 75 nM or less, 50 nM or less, or 25 nM or less.

20. A compound according to any of the preceding claims for use in medicine.

21. A compound according to claim 20 for use as a protease inhibitor.

22. A compound according to claim 21 for use as a cysteine protease inhibitor.

23. A compound according to any of claims 20-32 for use in the treatment, prophylaxis and/or diagnosis of inflammation, type2 diabetes, asthma, severe influenza, respiratory syncytial virus infection, CD8 T cell inhibition, inflammatory bowel diseases, psoriasis, atopic dermatitis, Papillon Lefevre syndrome, Haim Munk syndrome, gum disease, periodontitis, rheumatoid arthritis, Huntington's disease, Chagas' disease, Alzheimer's disease, sepsis or for application in target cell apoptosis.

24. A pharmaceutical composition comprising, as an active substance, a compound as defined in any of claims 1-23 or a pharmaceutically acceptable salt thereof together with a pharmaceutically acceptable carrier or diluent.

25. A pharmaceutical composition according to claim 24 in unit dosage form, comprising from about 1 μg to about 1000 mg such as, e.g., from about 10 μg to about

500 mg, from about 0.05 to about 100 mg or from about 0.1 to about 50 mg, of the active substance.

26. A pharmaceutical composition according to claim 24 or 25 for oral, nasal, transdermal, pulmonal or parenteral administration.

27. A method for the treatment of ailments, the method comprising administering to a subject in need thereof an effective amount of a compound as defined in any of claims 1-23 or of a composition as defined in any of claims 24-26.

28. The method according to claim 27, wherein the effective amount of the compound is in a range of from about 1 μg to about 1000 mg such as, e.g., from about 10 μg to about 500 mg, from about 0.05 to about 100 mg or from about 0.1 to about 50 mg per day.

29. Use of a compound as defined in any of claims 1-23 for the preparation of a medicament.

30. Use of a compound as defined in any of claims 1-23 for the preparation of a medicament for treatment, prophylaxis and/or diagnosis of inflammation, type2 diabetes, asthma, severe influenza, respiratory syncytial virus infection, CD8 T cell inhibition, inflammatory bowel diseases, psoriasis, atopic dermatitis, Papillon Lefevre syndrome, Haim Munk syndrome, gum disease, periodontitis, rheumatoid arthritis, Huntington's disease, Chagas' disease, Alzheimer's disease, sepsis or for application in target cell apoptosis.

31. A method for modulating DPP-I levels in a subject in need thereof comprising administering to said subject an amount of a compound as defined in any of claims 1-23 or a composition as defined in any of claims 24-26 in an amount effective to modulate said DPP-I levels in said subject.

32. A method according to claim 31, wherein said DPP-I is inhibited.

33. A method according to claim 32, wherein DPP-I is selectively inhibited as determined by IC_{50}(Cathepsin B)/ IC_{50}(DPP-I assay) is 25 or more such as, e.g., 50 or more, 75 or more, 100 or more, 250 or more, 500 or more or 750 or more.

34. The method according to claim 32 or 33, wherein DPP-I is selectively inhibited as determined by IC_{50}(Cathepsin H)/ IC_{50}(DPP-I assay) is 25 or more such as, e.g., 50 or more, 75 or more, 100 or more, 250 or more, 500 or more or 750 or more.

35. The method according to any of claim 32-34, wherein DPP-I is selectively inhibited as determined by IC_{50}(Cathepsin L)/ IC_{50}(DPP-I assay) is 25 or more such as, e.g., 50 or more, 75 or more, 100 or more, 250 or more, 500 or more or 750 or more.